what we would like to see and compared to the 1.1 percent that the 6940, the approved bipolar lead dislodgement that when the 6940 was undergoing its clinical evaluation, its dislodgement was 4.3 percent and so I think there is certainly a learning curve for new leads but I will let Dr. Wharton address that.

DR. WHARTON: I would just like to reiterate that we have seen I guess three different types of atrial screw and defibrillation leads and I think there is a learning curve with each of those. We get, you are used to screwing an just bipolar pacing leads in the atrium but when you are asked to screw in an atrial defibrillation lead with the heavier element and the ability, the little bit greater ability to torque down, you have to be very sure about the active fixation and I think it is just one of those things that you learn as you give it more tugs and you make sure it is secure and it is clearly this sort of curve or one or two that you put in before you feel really comfortable that you have got a secure fix. That is confirmed by their numbers here and in the 6940 series as well.

DR. GILLIAM: One other question concerning your programming for your atrial slash fibrillation therapies. It is not clear, I do not actually use this device but you have your crossover between your atrial fibrillation and atrial tachycardia and there is a zone in between. Are the atrial tachycardia detection intervals, are they always longer than the atrial defibrillation detection intervals? What I am asking is are there

an interval that falls under atrial tachycardia but is not accessible by atrial fibrillation? How wide are your atrial fibrillation intervals?

Looking at the cartoon, I could figure out 270 milliseconds as the widest interval that you could program your AF detections on. I just wonder if that was correct. In other words, must you program an atrial tachycardia? Someone who has either AF or nothing, do you have to program an atrial tachycardia zone?

DR. STANTON: I believe not. The range that you could program the AF interval, the AF interval has a fixed, fastest cycle length of 100 milliseconds, can then be programmed up to 300 milliseconds. The AT can be programmed down to as fast as 100 milliseconds or as slow as 450. You can program it so that there would be separate AT and AF zones or you can program an overlap.

DR. GILLIAM: Okay, if you program your AT down to 100, that essentially means you don't have an AF zone. Is that correct?

DR. STANTON: Correct.

DR. GILLIAM: Are all the therapies available for AF available for AT?

DR. STANTON: Yes, but not the reverse.

DR. GILLIAM: Yes, I understand not the reverse. So I would program, could I program to skip the 50 herz therapy? In

other words, do AT pacing and immediately go to AF defibrillation?

DR. STANTON: You could go from anti-tach cardiopacing with a shock without programming high frequency burst, yes.

DR. WHARTON: Could I make this kind of one comment because you sort of alluded to this in the course of your question, and we showed data in this regard and I think it si really fascinating data. If you recall, most of these patients had afib predominantly, a quarter or so patients had other atrial tachyarrhythmias. But when you actually look at what was recorded by the device, most of the patients had episodes of what would really be classified in the atrial tachycardia type of range which I found absolutely fascinating and may even get back to some of these mortality issues that we are talking about in terms of the burdens and arrhythmics that these patients have that perhaps we are not aware of. But that is important for having that atrial tachy range in there so you can treat those short of giving a painful shock.

DR. GILLIAM: I think to that end I am sold pretty much that the shock therapies ultimately work I guess. I am not sure that we have enough data here to say that we can do that with this device yet but I think I am convinced that atrial anti-tachycardia pacing works. I would like to direct a couple of questions toward particularly the 50 herz therapies and I don't think we have the data that suggests, I mean, there are 31

conversions out of 100, 33 odd episodes and I think that area is sort of lumped in if you will with the anti-tachycardia pacing therapies to give you your 50 percent confidence. I mean, it gives you a 50 percent success range. If we were to look at each of the therapies for atrial arrhythmias as shock, the anti-tachycardial pacing and then your high rate pacing. Your high rate pacing does not meet your threshold and I just wonder, where did it come from and what are the implanters? Do you guys use that at all?

DR. STANTON: Let me just set this up and then ask them to comment clinically. Overall, for all the times high frequency burst was used for all tachyarrhythmias, it was successful 24.6 percent of the time. Now, what are the implications of that?

DR. MARKOWITZ: Our philosophy was to employ the 50-herz pacing and the rationale was to provide an incremental yield in terminating atrial arrhythmias. The safety issue is important as you have both alluded to and we felt comfortable that with the back-up mechanisms, as a ventricular defibrillator it was safe and therefore it was useful to employ the incremental yield.

DR. STANTON: I guess what I am thinking, if you have atrial tachycardia, a lot of us know in the lab sometimes atrial flutter is pretty darn tough to get somebody out of and a lot of times we were right in the afib and then afib gets converted. In that way I guess, if that is the logic, I am somewhat, I guess from the implanters, it is somewhat not surprising to me that it

has a low successful termination of AF. I would be shocked if it every did it, frankly.

DR. WHARTON: I was just going to say that. I mean, what is amazing to me is the fact that it has a 20 percent efficacy. But that is great when you look at what your next alternative is beyond this point and that is giving a shock that is going to be painful to the patient. So again, anything that we can do to decrease the frequency with which we are having to deliver shock therapy for atrial tachyarrhythmias is a step forward, even if it is maybe just a small increment of 20 percent but still that is surprisingly good I think.

DR. HARTZ: Again, coming from a surgeon, my questions hopefully will be a little more simplistic although I will get back to your famous table at the end.

A concern that I have in general for the population of patients having defibrillators is the issue of lead compatibility so on the labeling you have listed all the nicely appointed electronic leads that are compatible with the device and the two connectors that are available. However, I would be more interested as a clinician in knowing which connector to use with which lead from another company. The reason I say that is because this nice, small device is probably going to be adopted very quickly by a lot of implanters and there are going to be some leads from other companies and I would like to see those listed in the labeling brochure. And then in small towns it may

be that they have to be ordered ahead of time.

DR. STANTON: If I could make a quick comment on that, that is probably a bigger issue than I am going to be able to address that a number of years ago was a very big issue for FDA. I think that this panel participated in discussions on that issue and maybe I would ask for, I don't know if it is appropriate but FDA may want to comment on that whole issue.

I agree with you from a clinical standpoint. We did not assess that obviously with any competitor's leads so we don't know about -

DR. HARTZ: I am not talking about universal competitors, I am talking about labeling for protecting the patients. I am suggesting to FDA that that get added to that labeling.

A couple of other small things. Can this device distinguish sinus tachycardia from atrial tachycardia? I mean, is this a rate cut-off phenomenon. Are we going to be defibrillating patients in sinus tachycardia?

DR. MEHRA: Again, the device has an algorithm called the PR Logic and one component of the PR Logic is what is called the sinus tach rule. Basically what it does, it looks for the one-to-one AV conduction but it is a ceratin requirement of what the timing between the A and the B has to be so what it does is it takes the V to V interval, splits it in half, and if the A to B interval is within that half, off the R to R interval, it calls

that a sinus tach so it has to be a one to one conduction and it has to fall within that window of AV conduction. Then it will call that a sinus tach and if the PR logic rule and the SVT rule is turned on, it will withhold therapy.

DR. HARTZ: Can this low energy atrial defibrillation cause ventricular tachycardia?

DR. STANTON: It did not in the 146 patients had 1,072 shocks delivered and in none of those cases did it induce a VT or a VDF.

DR. HARTZ: Okay, those are the easy issues. Now just a couple more major things. I am not convinced that a nine-joule defibrillating threshold is always going to be acceptable. Will there always be a higher energy device in the room for when the testing is done? You have six percent of patients in a series that has greater than 70 percent ejection fractions and I didn't read the data carefully enough to see which were in the 60 and 50 percent range but if you take a group of patients that has less than 30 percent ejection fractions, I can visualize that a fair number will not be successfully rescued with only a nine-joule threshold so I just want to make sure.

This device, as you have set it up appears to me that it is going more towards an atrial device but yet your data has to do with ventricular tachycardia patients so I would want to make absolutely ceratin that that was not the only device in the operating room when one was doing the testing.

DR. STANTON: I agree completely with you. We currently market a device that has 35 joules delivered energy.

DR. HARTZ: And then finally back to this table. The same, thing, when these slides flashed by, these stood out like sore thumbs. You don't have to put it back on but I can envision you probably should have included the demographics and hemodynamics on those patients who died in both of these two groups because again, you had a group of patients with a very high ejection fractions. If we knew about this small group of deaths, we could decide for ourselves if the mode of death had anything all to do with the device. Probably did not. Probably the VT/AT patients were not quite as sick as the VT patients. It just doesn't make sense any other way to me.

DR. STANTON: It is almost unfortunate that there was a benefit. I say that somewhat tongue in cheek. We seem to have stumbled into a hornet's nest with that finding. That was an unanticipated finding. We did look at other factors, including ejection fraction which did not separate out as a predictor. We can go through the whole list if you want.

DR. HARTZ: You mean you took the small group who died, these two small groups. There could not be enough in these two groups to be statistically significant based on ejection fraction. Even in a univariant sense I don't believe.

MR. JOHNSON: The patients who died did have a lower ejection fraction. However, it was the same in both whether the

50 or the Gem DR or the Jewel AF. The patients who died did have lower ejection fractions but overall the comparison of the two groups, we didn't see any difference in the ejection fraction between the two groups.

DR. DOMANSKI: Isn't it fair to say in another way that the outcome is independent of the ejection fraction?

DR. WHARTON: Can I make a comment? And again, this is not to get weighed down in this because this is really a side issue I think for this device but in terms of a possible way in which afib suppression would limit mortality. If you look at the deaths that occurred, it is mostly heart failure deaths. You never know how much of that may have been infarction death. There is a plausible mechanisms and again this doesn't prove it, it is more just an interesting hypothesis that perhaps needs to be tested in the future. An afib can cause worsening of heart failure, it can cause exacerbation of angina. Those in and of themselves can set off a cascade of events that can result in non-sudden cardiac death or even potentially sudden cardiac death.

And perhaps this device is limiting that way. Again, not proven by the state, I am not trying to say that.

DR. DOMANSKI: But Mark, would we be able to look at your defibrillator at your terminal event and determine whether you had a higher percentage of people who were in afib?

DR. GILLIAM: I am not sure they would have to be in

afib at the time they die.

DR. WHARTON: They wouldn't have to be in afib but with the thing programmed off being a better outcome, it is a reasonable speculation for future research but it has little to do with approval of this device I think.

DR. HARTZ: Since you mentioned mode of death, isn't the two year survival or two year freedom from sudden cardiac death in a patient with a defibrillator, isn't it supposed to be in the mid-90 percent?

DR. STANTON: Freedom from sudden death is typically up there.

DR. HARTZ: If you look at Doris's data, the FDA data that was presented to us, you have something like an 8.7 percent mortality at six months or looking at freedom from 1993, six months similarly here. Total mortality. So that is not approaching what we expect at two years and one would conceive that the six month figures are mostly arrhythmic deaths or they should have been getting a device in the first place.

DR. STANTON: No, I am not following that but let me make sure we are on the same wave length. The two year survival that you are quoting of greater than 95 percent, that is freedom of sudden death, that is not total mortality. Very unusual for a defibrillator study to show at two years a total survival greater than 95 percent. As you point out, this is a very sick population general. In most studies it is 35 to 38 percent.

DR. HARTZ: Yes, but we need to know the modes of death here because at six months they are, I mean, are we putting devices in people who are that close to death, especially if there is a high number with good ejection fractions?

DR. STANTON: Included in the report, overall there were 26 deaths, four of which was sudden cardiac death but again the analysis we did was total mortality. I am sure if we had just done the four, looked at just the four sudden cardiac deaths, freedom from death at six months would be much higher.

DR. HARTZ: It just gets back to my whole concern with the whole issue is that are we going to be putting in too many devices early on because they are small and there is so much atrial fibrillation and are we really going to be doing the pouplation a lot of good if we are not changing mortality in six months?

DR. STANTON: That is a very reasonable question to ask. I think that one of the things we found from this study also which is confirmatory with a lot of data that has come out in the past year independent is that what we have shown in both the Gem DR and the Jewel AF is the people with a history of approximately 2.5 times increased risk of total mortality compared with patients who did not have atrial arrhythmias, confirming the independent nature of it so I think you are right in observing this is a sicker population than the non-AF patient group.

What we would like to proceed to do is then see does it

impact on mortality and this study was not designed to address that even thought the intriguing finding of a possible decrease that we are not even asking for labeling for, it was just an intriguing finding.

DR. HARTZ: That is all I had.

DR. SIMMONS: I guess Dr. Gilliam has a few more questions and I have some more questions and we are past the time for a break so let's take a 15 minute break.

(Brief recess.)

DR. SIMMONS: Okay, let's get started. Dr. Gilliam?

DR. GILLIAM: I just have one questions and it is just I think it is important for us to note the characteristics of the atrial fibrillation on patients who were selected for this study. They had to have two episodes of afib within the year previous. Is there any description of afib that would give me some enlightenment? I mean, are we talking about people with recurrent, persistent afib that had to be intervened with by shot or just any episode of afib, say on a Holter monitor that was asymptomatic that was self-terminating after, say, five seconds?

DR. WHARTON: I can't speak from the data but I can speak from experience and that is all, I can't think of an exception, all of our patients had sustained afib requiring some kind of intervention, electrocardio version or pharmacologic cardio version to terminate.

DR. MARKOWITZ: Similar experience here as well.

DR. STANTON: At least one of the episodes had to be by electrocardiogram, not by Holter so presumably the person had to be sent for the ECG or could have just had it at the same time.

DR. GILLIAM: I guess the threshold, though, that is given by at least these two centers was just that they actually required an intervention to terminate at least one or maybe even both the episodes of afib. Is that in general true of the rest of the centers that the afib that qualified them for entry was an afib that required an intervention, either pharmacologic or -

DR. STANTON: We don't have those data. The entry criteria was two documented episodes, at least one of them being by 12-lead electrocardiogram, not Holter. Sorry, beyond that we don't have it.

DR. MARKOWITZ: I would just clarify my comment. We didn't require intervention at our center. We required sustained episodes.

DR. WHARTON: Also I might just comment. Given the patient pouplation for this specific trial compared to, say an afib only type of study, the fact that there is such a burden of heart disease in this group of patients that may go into fib, they tend to sty in fib unlike the lone fibbers or the people with minimal heart disease.

DR. SIMMONS: I just have a few questions or issues. I guess first, going back to this HO lead. If the HO lead, if the 6943 didn't improve your defibrillation thresholds, and it has

the potential to do harm, why do you even want it? Why are you including it? I mean, it has the potential to do harm and if you haven't improved your defibrillation thresholds, why not just use your regular HO lead and your regular two coil ventricular lead?

DR. STANTON: The Jewel AF has systems that are built into it that minimize the chance of harm. Number one, it has, it is a full ventricular defibrillator.

DR. SIMMONS: If the people have gotten shocked, you have already seen that. Go ahead, I am sorry.

DR. STANTON: One person had VF induced by it when it dislodged. That was 15 minutes after implant.

DR. SIMMONS: But you have already, one of your representatives already said that if the atrial lead did dislodge, it is conceivable that ventricular defibrillation would be ineffective so it has the potential to do harm.

DR. STANTON: It would depend on how the device is programmed. When many investigators programmed the RV and the RA coils, to the same polarity and then the can to the opposite, then in that case it would not short out the system. I think that the rationale for people wanting to place it in the atrium, and this was at the physician's choice, 97 times people chose to do that, one of the rationales for that is some people feel very strongly about true bipolar sensing in the ventricle. I was one of those when I practiced and so I think that being able to have true bipolar sensing in the ventricle, you can't have an SPC

today except for an investigational lead that we have, you can't have an SPC coil.

And so to put in a separate atrial shocking coil, it is better for the clinician to be able to put it on the base sense lead.

DR. SIMMONS: I guess I am going to have trouble being comfortable approving a device that is designed to be a lifesaving device that you are modifying it to treat a non-life-threatening arrhythmia with a device that is potentially going to negate the lifesaving potential of the device. What would you say about the idea that most lead dislodgements occur in the first 24 to 48 hours, certainly in the first month that is a warning or a precaution or a recommendation at the very least that the atrial tachyarrhythmia section not be turned on for the first month. What do you think about that?

DR. WHARTON: What do I think about it? I don't think that it is necessary. Certainly we don't do that and we are concerned about the longevity of our patients as is everybody here. And again, I think the issues are with the device is that the atrial tachyarrhythmia therapies if they do as the one example they have and do something such as BF then you have a way of treating that appropriately so make sure that the atrial leads are in so it doesn't fall down. We use usually the RV SVC coil so it is not an issue anyway. I don't think you have to mandate not turning on atrial tachyarrhythmia therapies personally.

DR. MARKOWITZ: I have to tell you what we practiced clinically in terms of enabling these therapies. We didn't as I mentioned, employ the 50 hertz pacing and programmed that at implant and the rationale was as following. We felt that the incidence of lead dislodgement was quite low. We felt that the likelihood of over-sensing and therefore initiation of therapy was also quite low and therefore the induction of arrhythmia was really extremely low and we had a back-up ventricular defibrillator to provide that safety net and that was our rationale in the clinical study in terms of programming those therapies on initially.

DR. SIMMONS: Just being the devil's advocate here, just as in the clinical study the 6940 lead had a four percent and it went down to one percent and the trial, this lead has a five percent, it could go up to 10 percent in a regular open trial. I mean, it could go just the other way. You are an experienced academic center, I mean, when it gets into regular general use, what if I were to tell you this lead has a 10 or 12 percent dislodgement rate? Would that make a difference on how you program this thing?

DR. STANTON: I am going to check something statistically. I think 12 percent is a bit above the 95 percent confidence bound probably with a five percent during clinical. So it has got a nine percent dislodgment rate. Would that change how you want to program the device?

DR. WHARTON: Sure it would but we are talking about theoretical and not things that have been shown clinically to be the case. I mean, as in most things we do in medicine, we are basically not clinical experience. It just has not been an issue with this device.

DR. HARTZ: His point, though, is a very good one if you are taking the best of the best putting these in in the trial and then expanding it to open use. I don't think you can use your confidence intervals in that situation. It is a different group of implanters.

DR. STANTON: But frankly, in every clinical study we do make these assumptions and we expand the data that we get in the clinical to the general pouplation. That is how the FDA makes approvals.

DR. DOMANSKI: It is also hard in clinical trials and clinical research in general to factor in incompetence.

DR. BRINKER: Marshall, in one of your statements somewhere along the line, you suggested that perhaps atrial defibrillation should be delayed until the leads stabilized, the atrial leads stabilized. Somewhere in here it says that, in one of your things. I can't remember exactly where but it does and the question is, maybe one of the guys who wrote it can explain how long it takes to stabilize.

DR. STANTON: I think what you may be talking about when one of the PR Logic, parts of the PR Logic algorithm. The other

one to one SBTs which is something that in the Gem DR and the Jewel AF we recommend, quote, waiting until the atrial lead is stabilized.

DR. BRINKER: How long does it take?

DR. STANTON: My personal opinion, one month. Let me hear others.

DR. GILLIAM: Specifically looking at AV and RT, how would you handle patients with that when it is very probable that the atrial activation is going to occur during what would be an effective blanking period of a sensitive events in AV.

DR. STANTON: Our defibrillators do not have cross-chamber blanking for a sensed ventricular event so we sense during the entire, the atrial channel is continuously sensing when there are ventricular events, not ventricular paced but a ventricular sensed event so in AV and RT, we would be able to see that and that is what the one to one SVTs rule is there for.

DR. SIMMONS: Okay, how about this. My own opinion is that a six joule shock hurts a lot. I have not seen very many people who do not think a six joule shock is perceived as significant pain. There was not an equality of life assessment done with this was there?

DR. STANTON: Yes, it is in the panel pack I believe. I can review that if you like.

DR. SIMMONS: I didn't see that. Did you have anybody who did not perceive a six joule shock as pain?

DR. STANTON: I don't think that specific question was asked.

DR. SIMMONS: I doubt it. All the other defibrillation studies for anti-tachy pacing and low energy shocks for VT, more than a joule is almost always perceived as pain. I mean, shouldn't we have some guidelines in the device that would suggest that how often recurrent episodes of atrial fib occur, that this device is not going to be useful? I mean, if a patient has atrial fib daily, then implanting this device is of no value.

DR. STANTON: I think that that is going to vary a lot, patient to patient, situation to situation. There are some patients that I personally know of that do accept a shock for termination because they are so symptomatic in their atrial fibrillation. There are other patients who never want to have a shock for termination of atrial fibrillation. I think the clinician needs to make that decision. Steve or Marcus, would you comment?

DR. WHARTON: Also putting in a guideline like that, I mean, the patient may at the time of implant be getting frequencies that are too acceptable but the plan is or he is being loaded with amiaderone or something that is going to decrease the frequency so I think you have to leave the clinician to his own judgment about what is appropriate because if the patient is unhappy, it is the clinician that is going to be hearing about it.

DR. SIMMONS: Yes, I am just saying not as a, I mean, even in the indications for the VF defibrillator, recurrent episodes of VF are a relative contraindicator or recurrent episodes of VT are a relative contraindication until those episodes are stabilized. I personally think some statement ought to be in there just as a guideline that frequent recurrent episodes are a relative contraindication.

DR. WHARTON: I guess the issue would be though you may have somebody that you are implanting because you are treating their ventricular tachyarrhythmia and at the time of implantation the atrial tachyarrhythmia rate may be too frequent but your plan is either to go in and treat it pharmacologically or do some type of maze procedure or whatever it is you are going to do to increase the frequency so you are anticipating the usage of the device later once you control the -

DR. SIMMONS: But still it is a relative contraindication, it is not an absolute contraindication.

DR. HARTZ: How long would that device last if this patient was being defibrillated from atrial fib every day?

DR. WHARTON: I think the bigger question is how long the patient would last.

DR. HARTZ: But I means seriously, what we talked about with the first devices. They would last 100 shocks.

DR. STANTON: It depends on what the output would be. Correct. The more the device is used at higher outputs it is

going to go out more quickly. But I think there are other issues that are involved and Marcus has pointed out some of them. There is the issue of atrial fib, begetting atrial fib and does atrial defib beget sinus rhythm? In other words, atrial remodeling. We didn't address that at all in this study but I think that that is a question clinicians have to raise.

DR. SIMMONS: You did have a certain percentage of patients who got coronary sinus leaks but you didn't present those defibrillation thresholds. Did that help?

DR. MANDA: There were very few patients who had a coronary sinus lead and comparing the patients who had a coronary science lead versus those who did not, the defibrillation threshold is well lower when they used a coronary sinus lead. It was four joules mean compared to 7.5 joules with a non-coronary sinus system but they did not reach statistical significance.

DR. GILLIAM: Okay, how many of those, of the coronary sinus leads were there?

DR. MANDA: There were six percent total so I think it was 18 patients.

DR. SIMMONS: I think I should pass and let our consumer rep, Mr. Dacey, have a chance. Do you have anything you would like to add?

MR. DACEY: Not a whole lot. Every time I attend a meeting I start a new learning curve. I guess I am an atypical consumer but when I go back and meet with the various

constituencies that I have to deal with, early in my training for this I was told about all the safety and efficacy issues. One of the things I can communicate is all the hard work and all the science that in fact takes place for the benefit of the consumer and I don't think the consumer in general has any picture of this whatsoever so if I am a messenger to the consumer, that is the message I carry. I only wish my wife were here because she taught statistics some years back and that would be helpful to me and I would only anecdotally add, as I was telling the doctors earlier, yesterday was my wife's 23rd anniversary of the implant of her mechanical mitral valve and she is just doing very fine.

So we have a very personal interest in this work and all I can say at this point is keep adding to my learning curve.

DR. SIMMONS: Thank you. Does anybody have any final questions they would like to ask? Does FDA have any questions they would like to ask as a final or comment?

Maybe we should start off by just going through the FDA questions. The first question. Are the clinical data adequate for the evaluation of safety and effectiveness of the atrial termination and treatment therapies in the model 7250 Jewel HO defibrillator.

DR. BRINKER: I think they are but I would like to append the comment that the clinical utility piece is missing. I mean, they have documented quite nicely that they can convert atrial tachycardia and atrial fibrillation reasonably

efficaciously and in doing it, it is relatively safe, very safe in fact, but the clinical utility for the patient of doing this remains undetermined in my point of view.

DR. GILLIAM: I think they demonstrated that it is safe at least in their hands. I am not sure they have demonstrated it is effective. I mean, if it is effective, you want to count I guess at 50 percent, is that the threshold we would say for effective therapy?

DR. BRINKER: That was the threshold but the actual numbers for tachycardia and for atrial fibrillation were higher than that based on the last therapy delivered.

DR. GILLIAM: The therapies.

DR. BRINKER: Yes, so I think it is effective in terminating the rhythm with reasonable success. I mean, it is not 100 percent effective but it is effective. I think that the issue is, is it clinically useful to do this on everybody that has an atrial arrhythmia and that is going to take a lot more kind of intense study and larger clinical trials.

DR. GILLIAM: But I don't think that the sponsor is making a claim for that. I think, I guess I am getting basically are these data adequate to say that this device is safe and effective?

DR. DOMANSKI: And said another way, I guess the question, I am not sure of the answer to it but I hope the panel will come to it, I guess I wonder whether or not this device

really, whether adding the complexity of something whose clinical utility is undemonstrated really gives you a device that is as good as one that doesn't add it and I am a little worried about that.

DR. SIMMONS: I guess if you were to view this as a ventricular defibrillator, as a defibrillator for ventricular arrhythmias, and say is it safe and effective. I think probably it is. I didn't see anything that is really very upsetting in there but the issue then is, is it also safe and effective for atrial arrhythmias. It is probably safe, is it clinically useful? I don't know.

DR. DOMANSKI: But you do add complexity when you do this and if the complexity is added for no clinical utility, then you have a device that is probably not as reliable.

DR. GILLIAM: And I am not so sure that we can't own its own, say that this device as a pure stand-alone ventricular defibrillator is safe. There are some variances between it and the Gem DR. I mean, the amount of energy delivered is less. It uses a different lead arrangement than the studies we have shown to us. Now, I think those differences may in fact be not significant. I don't think the investigators here at least seemed to think they were. I do think that that is a consideration, that this is, and I keep coming back in my mind thinking that this is not an approved ventricular defibrillator that has a few bells and whistles that the whole system is

something unlike that we have seen before so in that way I keep coming back to me, I don't, I mean, do we have enough data about this device to say that it is safe and effective?

I guess this question specifically looked for atrial arrhythmias and they don't question whether the device itself in total is safe and effective. I want to make sure we don't make the assumption that it is an effective ventricular defibrillator and gloss over that issue.

DR. BRINKER: That issue is paramount as far as I am concerned. I think that they do have, if this didn't have any of the atrial therapies involved in it, but this was a smaller defibrillator that was top rated at 27 joules, the data that they present compares very favorably in VT/VF only patients to that of the Gem, the predecessor and quite frankly, I don't have, I think they have met the test for ventricular tachycardia fibrillation safety and efficacy if it didn't have all this other stuff involved with it.

So now let's take in this other stuff and let's take the questions one by one. In my opinion, safety and efficacy for atrial termination is proven. The clinical utility for this indication is not. This is not an indication actually so I would pass on this question saying they have done enough to say that this could be done and I think that the labeling should have whatever disclaimers that this, this benefits a specific patient.

DR. SIMMONS: I think that is a good suggestion and if

we go to the indications slide, the label in question, indications for use and then argue about that for a few minutes. Want to try that? Let's go to the next slide. This is do the following indications for usage adequately define the patient population study? Indications for usage. Patients who are at risk of sudden death due to ventricular arrhythmias and have experienced one of the following: survival of at least ... The model 7205 Jewel AF system is also designed for patients who either have or are at risk of developing atrial tachyarrhythmias but is not and we will leave out currently, it is not indicated for patients who do not have the BT/AF indications stated above. If we were to later throw in a sense there that would say something like the clinical utility of the atrial tachyarrhythmia device, has not been established.

DR. BRINKER: I would take out that word currently.

DR. SIMMONS: I did.

DR. BRINKER: I spoke too fast. My mind was fixated.

DR. GILLIAM: Thematic criteria I guess or not in this still. We had that meeting -

DR. SIMMONS: That is another issue. They don't get to use that, remember?

DR. GILLIAM: I am just wondering. We still haven't resolved that yet.

DR. SIMMONS: That is a political issue.

DR. HARTZ: There is a problem here. Indications,

patients who are at risk of sudden death due to ventricular arrhythmias and then note clinical outcome for hemodynamically stable VTP is not fully known.

DR. SIMMONS: Oh, no, that is because -

DR. GILLIAM: Hemodynamically stable VT is not known.

DR. SIMMONS: That is on every defibrillator. If you have clinical stable VT, there is a lot of argument about do you need a defibrillator. If you are hemodynamically stable, there has been a lot of argument but there are some people who still feel that -

DR. HARTZ: I see, poorly tolerated VT. Okay. So that goes on every one?

DR. SIMMONS: That is a pretty standard introduction to every defibrillator. Does that make you feel better if we were to throw a sentence in like that at the end of the indication section? Rosie? I am not as concerned about the, I don't know, I can envision in any complex device that the software is going to get screwed up. I just don't trust, I started out as an engineer and I just know that they are convinced that they have got this software worked out but I am as convinced that it is going to, that there is a hole in it that we are going to figure out sooner or later so but at the same time, I think that as a defibrillator, this is probably as good as you are going to get at this point in time as far as ventricular defibrillator. The question is, is it going to add anything to the clinical?

DR. GILLIAM: I don't have, I mean what was your sentence again?

DR. SIMMONS: I just threw that out. Something like at the end of it saying the clinical utility for atrial defibrillation tachyarrhythmias has not established.

DR. GILLIAM: Okay, I think yes if you put it down with essentially the other note and the same disclaimer made for VT, the equivalent sort of statement for AF, atrial tachycardia may be acceptable because I don't, I guess I get coming down to it the fact that I don't think we have demonstrated any clinical utility.

DR. STUHLMULLER: I guess from a regulatory perspective what I would like to point out again is if you look at the panel recommendation options, in order for an agency to approve a device, it has to be both safe and effective and safety again is reasonable assurance that the probable benefits of how to help based on its indications for use outweigh any risk and efficacy again is reasonable assurance that in a significant proportion of the population the use of the device for its intended use provides clinically significant results and that is what you need to -

DR. GILLIAM: I don't think this device is going to kill anybody.

DR. HARTZ: I disagree with that. I think this device is safe in the hands of electrophysiologists. This is what is

bothering me. I think the second this device is going to be put in, and it is so small and so easy to put in, they are going to have a lot of non-educated cardiologists, I mean, even some general surgeons putting in this device, not programming it properly, not having the proper follow-up and I think it could kill someone.

DR. GILLIAM: I think that is probably true of any of the devices out there and that is more of the case.

DR. HARTZ: But this on is easiest. This is so tiny.

DR. GILLIAM: It is not actually smaller than many devices that are already out that are already approved.

DR. DOMANSKI: You know, I have some doubts about whether this thing should be approved but I have a problem with disapproving it based on elegant design.

DR. HARTZ: What I am saying is I don't think you are going to keep this device at a very broad application for more than a week.

DR. DOMANSKI: I don't think that is a basis for disapproving it.

DR. STUHLMULLER: Again, the intention, what the panel needs to do is focus on whether it is safe and effective for its proposed indication for use. Now, you potentially have the prerogative to revise the indication, what you believe should be an appropriate indication for use and then say whether it is safe and effective for an alternative wording to the indications for

use but you can't factor in the potential off label use of the device until your recommendation.

DR. BRINKER: Let me remind the panel that when we first looked at rate adapted dual chamber pacemakers, we approved them because they were safe and effective for pacing the patient but that initial approvals of devices before the ventilation device carried with the rate responsive characteristic that was not proven to have any clinical utility.

So I think that certainly this device is safe and effective and it meets your standard criteria of approval and it may have some other capabilities whose clinical benefit is not yet proven but that should not bear the standard of carrying a clinical utility proof at this period of time.

DR. STUHLMULLER: I think what you are trying to get at is the issue that devices are marketed without any claim made for certain features. Is that what you are trying to get at?

DR. BRINKER: Yes, devices can be approved and then marketed without specific claims.

DR. GILLIAM: I think what Jeff is saying, I agree. What you are saying, in effect, that this device is efficacious at terminating atrial arrhythmias and I think that the studies have suggested that maybe 70 percent of the afib at least would shock and I am willing to buy that. I am not so convinced that it is a 50 herz type thing but I will buy the shock in the atrial tachycardia. It does that. Now, I don't think we have to put the

burden on the sponsor at this time to demonstrate that terminating or decreasing atrial fibrillation brings a benefit to the patient. I mean, they are not claiming that if you have less afib you will live longer, live better, do whatever, but they are saying that the device is indicated for people who have atrial tachycardias and there may be some benefit there. Implied, but I don't think the company is making that claim.

DR. DOMANSKI: Well, of course, I guess the question is, I guess this is the question for you, John. If the device is safe and effective for terminating VF or VT which we know it is, are you willing to accept approving a device for which no clinical utility is shown for other major features of it? I mean, I just don't understand the law because if the question is, is it safe and effective for terminating atrial tachyarrhythmias is does not. What about VF? But there is no clinical utility demonstrated right now. I think that is a very interesting issue.

DR. STUHLMULLER: I am going to let Dr. Sapirstein answer that but I guess one preface would be I am not sure I understand what you mean by clinical utility.

DR. DOMANSKI: I mean, clinical utility. I mean, is it used, I mean, if you had a device that was safe and effective for chopping off someone's head, you probably wouldn't market it. That is not exactly the thing but here, it is already patented. Here you have got a device that will do something to an atrial

tachyarrhythmia. Right now there is no demonstration that is a useful medical maneuver. We are interested in that. That is an interesting question but there is no demonstration that that is a useful medical maneuver at this point and all I am asking is whether or not you need safety and efficacy for something that has some clinical utility and if the answer is no, then this is a great cause.

DR. SAPIRSTEIN: Well, Michael, to extrapolate from what you said, we are willing to approve a device if somebody says they have a device that will color a tumor pink, we won't approve it if there is no clinical utility. Your recommendations based on safety and effectiveness for doing what it says it does and whether it is a defibrillation of the ventricle or defibrillation of the atrium, that is what you base it on. If you think there is no utility to defibrillation of the ventricle then you shouldn't approve it.

DR. DOMANSKI: OR defibrillation of the atrium in this case?

DR. SAPIRSTEIN: Yes, you shouldn't approve it but if the device as a whole does what it says it does and you think there is not harm to it, it is safe and it is effective in dealing with it then your recommendation should be submitted.

DR. STUHLMULLER: And again, what you need to do is work within the context that safety is defined as reasonable assurance that there is probable benefit to health versus the risk and that

effectiveness is, does the data provide reasonable assurance of clinical benefit in a significant portion of the population and that is the way you should operate within that construct in terms of how you make a recommendation.

DR. BRINKER: I would like to remind us that this is primarily and actually solely indicated for patients with VT/VF and that the add-on features may or may not be applicable but the primary indication is for, even if they are, in other words, if this device was solely being indicated and/or marketed to patients with atrial tachyarrhythmia with VT/VF back-up then I think they have failed to meet the burden of acceptability but since it is the other way around, I think they have.

DR. SIMMONS: Because the indications, the way they have worded their own indications, don't even mention atrial defibrillation. So I think based upon the fact that they are marketing a defibrillator with a feature -

DR. STUHLMULLER: I guess the question is would you agree that there is two aspects of the indications for use. One has to do with a standard type indication for VT and VF and that there is a second aspect to the indications for use related to the specific features I would discuss today and is the indications for use for that portion, does the data set that you have before you support what has been proposed as an indication for use?

DR. GILLIAM: One thing before this, I would like to

strike out in that atrial fib who have the or are risk of developing. I think that that is a very inaccurate, I mean, I would as soon not have that in there because essentially anybody is at risk and that doesn't really say anything.

DR. BRINKER: I wouldn't want to take that out because that would mean that if, that would limit the use of this thing to only people that have had documented atrial arrhythmias. I think that this is primarily, let me just give you a correlate. Why don't we put on rate-adapted pacemakers only patients who have heart rate, heart control picking confidence.

DR. GILLIAM: But even if you don't put that on there, I am not saying that you put on every one that it is only implanted in people who have confidence. I mean, you basically implant a device and you program it the way you want. I don't think that if you put out, it is designed for patients who have atrial tachycardias. If you don't say who are at risk of developing, it doesn't say that you have to show that they have atrial tachycardia then, I mean, it does say that you have to show ventricular tachycardia to get it but it doesn't say you have to show atrial arrhythmics to get it.

I think there is a difference in indication.

DR. BRINKER: So how would you write it?

DR. GILLIAM: I would just basically, I just think if you leave in who are at risk of developing atrial tachycardias, that sounds, I mean, who is not at risk of developing

tachycardias with ventricular tachycardia? Is there any patient that you have who has ventricular tachycardia who is not at risk of developing? I guess the one person may be the person who already has AF that is chronic but you can't get out. They already have it. So I don't -

DR. BRINKER: That would be actually, that point is perhaps the best point and that is the patient with atrial fibrillation that can't be -

DR. GILLIAM: I looked under contraindications but I would just take out that, I just think that putting in who are at risk of developing atrial tachycardia, I just don't know who that excludes and I don't think the statement is necessary.

DR. STUHLMULLER: I think in terms of trying to keep the discussion focused, I mean, Dr. Gilliam, is one of your points that there is a discrepancy between what the patient entry criteria were for the study versus what they are suggesting in the labeling? Is that a concern?

DR. GILLIAM: No, I don't think that is it. I just think it is unclear to me that that indication, when you put something that is very vague in an indication, when you basically say who are at risk.

DR. HARTZ: There is a discrepancy because the study was very clear about who, what their requirements were for the atrial fibrillation and this takes them back out.

DR. GILLIAM: I think that we often do things for a

study, I think we often do things in a clinical study that we may not have the same rigorous criteria for implant. I don't have a problem there. I guess what I am saying, I don't want to limit it but I don't want to confuse things, too. When you start to say people who are at risk, we might get a group of people who may feel that if you have someone who they feel is at risk of atrial arrhythmias implanting this even though that goes against the spirit of the device which is a ventricular device that we then focus on those people with atrial arrhythmias. I don't think it makes any difference. Maybe I am just beating on semantics.

DR. BRINKER: I mea, if you had a patient that had one episode of atrial tachycardia or one episode of atrial fib, didn't have anything else and you felt that this guy might be at risk or had a less than DF, -

DR. GILLIAM: I would want to put it in this box.

DR. BRINKER: You would want to.

DR. GILLIAM: Yes.

DR. BRINKER: Okay.

DR. GILLIAM: But that patient also has atrial tachycardia but if you want to put into my other habits, I guess I am, if you look at my personal habits, I probably put in all rate responsive pacemakers, whether the patients have demonstrated any competence.

DR. BRINKER: You don't pay attention to the labeling if they, all right. I think you have the gist of what we are

thinking and you can, the FDA can work on this with the company. I think the point is well taken.

DR. SIMMONS: Let's agree to leave out the word currently and can we agree to just move on? How about have we agreed as a group that we like the idea of putting in another statement to the effect the clinical utility of atrial tachyarrhythmia therapies has not been determined?

DR. GILLIAM: Yes.

DR. SIMMONS: We are up to three. Based on the clinical experience, should there be additional contraindications for the use of the model 7250 defibrillator. For example, should patients without ventricular arrhythmias be contraindicated for use with the Jewel AF ICD? The answer to that is yes. Are there other contraindications you want to use?

DR. CRITTENDEN: Chronic AF.

DR. HARTZ: We can't say chronic AF if the device is going to be used for VT in that patient, right?

DR. SIMMONS: But there is other devices.

DR. HARTZ: So we are going to say not to use this device in chronic AF.

DR. SIMMONS: What is a dual chamber device anyway? If you are calling the patient chronic VF, if you are saying I don't know and I want to take a shot at getting him out, then you have already said that they are not chronic in my mind.

DR. CRITTENDEN: Exactly. When I say chronic AF, I mean

somebody who is always going to be in AF forever and ever amen, and you have already made that decision. I mean, I know there are many patients who come in who have a persistent AF and I sort of think I can get them out of it, I may shock them, beat on them, do whatever at the implant and plant a dual chamber device. But I think that would be consistent with the other devices that are out on the market at this time. I don't think any of them are indicated for chronic AF.

DR. SIMMONS: Does anybody feel strongly about putting in a statement about patients with frequent episodes of atrial fibrillation that may result in unnecessary therapies? I will be outvoted on that one. Anybody else have any other contraindications they would like to add?

Several patients enrolled in the clinical study failed to meet the ventricular implant criteria and received a commercially available ICD with higher defibrillation energy. Should the instructions for labeling include a warning which advises the patients that the Jewel AF may not be appropriate for patients who require greater than 27 joules of fibrillation energy.

DR. BRINKER: Absolutely. In fact, there might be a statement to the fact that nobody in this trial had a DFT greater than 12.

DR. GILLIAM: I think this warning, that is pretty strong. I think if you talk to most electrophysiologists, when

you, I don't think anyone, you have to test it at implant. By definition if you test it and it doesn't convert them, it is inappropriate to implant that device and so I am just asking, are we making a warning to an idiot. If the thing doesn't work and you put it in, no warning in the world is going to prevent you from doing something stupid. This says less than its purposes.

There are several other devices that do not have 35 joules delivered energy and I do think that, I am getting confused about delivered versus stored because I think we have flipped back and forth so many times with this. This is listed as delivered energy and I think we are going back to delivered energy as opposed to stored energies now.

DR. DOMANSKI: I don't see how one can argue against putting it in as a warning, particularly if there are other devices out there that have a higher one.

DR. HARTZ: I think the number has to be changed, though, because they should not have a defibrillating threshold of 27. They should have a defibrillating threshold of 18.

DR. BRINKER: They didn't say DFT. They assume that they will factor in a safety factor which is, I think there should be a reminder somehow that this device is capable of delivering only 27 joules and that appropriate care should be taken to insure adequate safety.

DR. GILLIAM: I think you can note that it delivers 27 joules of energy but I know that there are several other devices

that were set to deliver 29 that were approved. I don't know that those devices had any specific warning.

You get on a little bit of a slippery slope because there are some investigators who don't say that you have to have a 10-joule, some people will say you have to have a 10-joule safety margin. Other people are a lot less rigorous than that. I am not sure you would find a consensus and I don't know that we have ever, here, with the devices that come through here, set such a threshold. I mean, I think there has generally been a sense of almost reasonableness that we get a device in that has been demonstrated to go through testing and use and be effective and safe clinically by the numbers of implants we have and I think that if -

DR. SIMMONS: But this is not going under a precaution or anything like that. This is just a warning and the warning section, it is just a warning that this device only has 27 joules and patients with higher DFTs should not be considered for this device or something like that. What do you think about that?

DR. BRINKER: His point, if it is true that this has not been brought up before as a labeling issue for defibrillators with similar outputs, it doesn't seem fair.

DR. GILLIAM: Exactly. I wanted to come with some consistency, I don't want to in effect, let something in the label that gives someone an unfair advantage that does things that their claims are not justified but at the same time I don't

think I want to necessarily be paying a company if it truly doesn't make any difference. If it does make a difference, then I think we have a problem.

DR. SAPIRSTEIN: We have a pretty well defined template for these devices and we can make sure that the labeling adheres to that conformity.

DR. SIMMONS: Let's go on to number five them. Considering the accelerations with the 50-herz burst and the non-successes reported for treatment in the AT and AF zone with the 50-herz burst as the last therapy delivered, are there clinical concerns or recommendations regarding the use of the 50-herz burst in reducing the number of accelerations and exclusively treating atrial arrhythmias?

DR. GILLIAM: I think that therapy is unproven by the data we have in front of us. I would be looking at the data now and inclined to suggest that that be locked out until we have enough clinical data to suggest that is it, I think that it is safe because I have a concern there because with lead dislodgements they have had at least one in this series where that particular therapy accelerated someone to VF. Now, granted, the device is functioned to work to save that particular individual but at the same time we all have many clinical people where that would be potentially, you don't always rescue people from VF. There are people that their VF is going to be their final event. And I would hate to have it because a device killed

them. I just think we don't have enough data from this.

DR. BRINKER: I think that this is, it is a disappointing modality at best but it works in a finite portion of people and it could be used to better advantage with more experience. What I would probably put in the label is some disclaimer that this can accelerate the atrial rate and I would also, we are not dealing with this right now, but I would also suggest that this be the subject of a post-market study or some mode of observation for this particular activity of the device. But I would hate to lock it out because if it prevents even in, if it prevents a shock, it may be helpful.

DR. SIMMONS: You know, I agree. I think that it is really unproven and I just wonder how many of those 24 percent of patients who got it would have just spontaneously terminated their atrial fib anyway since it is proximal atrial fibrillation. I guess I would like to see it in there but I would, what about a, did we address the issue of waiting a month or so or something until the atrial lead is matured before programming atrial therapies on? Does anybody feel strongly about that?

DR. GILLIAM: I am sort of inclined not to do that because I think when you put it in, I don't want to start dictating how people program a lot of the devices because there may be a good clinical reason why you feel very strong that you don't. I think this particular modality is, I don't think we, it didn't meet the threshold that we set which is a 50 percent. I

mean, half the time and it was 30 out of 130, 20 percent. I think that -

DR. SIMMONS: I am just not so sure how easy it is to lock something out. I mean, is that asking a lot or is that a small thing? Because if you change software programming then you have to recertify the software.

DR. DOMANSKI: You also don't have a lot of data to suggest that that is a useful maneuver.

DR. GILLIAM: I don't know that this particular event is, I mean, it has not shown to be efficacious by the criteria we set up. It may not be safe so I mean, this particular feature I think does not meet the criteria that I would feel comfortable today at least voting to have it go ahead because I don't think we have the data. It may turn out to be that this is a wonderful thing, I just don't think we have enough experience with it, at least I can say that today. Do you disagree, Jeff?

DR. BRINKER: I would like to see it not locked out. But I would like to see more data and that is not necessarily incompatible goals. Maybe the FDA can work out a way that that can be done.

I think, what if this turns out to have no real, by safety meaning no death, stroke or infarct issue and 500 patients who were programmed to it and converts atrial tachycardia short of a shock in 25 percent of those who would otherwise go on to a shock, would you consider that, again, 50 percent efficiency,

effectiveness, is not necessarily the goal of a single type of a therapy. It would be the goal you would want of all the tiered therapies. And this is only applied, I presume and people have already failed one therapy. That is the anti-tachycardia pacing so I am -

DR. SIMMONS: Yes, we don't even know ow many people, I guess I meant to ask that, of how many people where the 50-herz burst was turned on as the first therapy. Is that even an option? So I mean, I guess from that standpoint I guess I would hate to see it turned off. If you are not concerned about letting them use the atrial lead and the anti-tachy pacing and the shocking and everything else, I am not concerned about them leaving the 50-herz burst in there.

Let's go to number six. In one of the cases the burst lead was dislodged. Are there concerns in the way the labeling is written? Use caution in enabling the other one to one SPTs criterion until the atrial lead stabilizes.

DR. GILLIAM: That is more confusing than any single thing I have come across with this lead. I mean, if you put that in, I am getting confused. I would as soon have that gone. I mean, personally I think, I don't understand that. I don't know what stabilized means. I think that the caution that it admonishes you to be aware, if you don't know enough about the device to know that, then I don't think this caution is going to help you.

DR. SIMMONS: I don't have any strong feelings either way.

DR. DOMANSKI: I agree with him though.

DR. HARTZ: Leave it out.

DR. DOMANSKI: Leave it out.

DR. SIMMONS: Number seven. Some of the model 7250 patients were programmed using the device's atrial tachycardial therapy sequence which offered delayed atrial pacing and defibrillation shock therapies. Considering the number of non-successes for AT and AF episodes and the failure to defibrillate cases, could some of the failures be attributed to programming this feature? Are there other concerns or additional programming considerations regarding delayed programming in the VT/AT pouplation? Does the proposed labeling contain adequate information for the effective programming? Also, in light of the atrial DFTs, are there considerations about programming the energy of the first atrial shock?

I mean, I think these are all the points that we are bringing up that we want to put in there that we don't know what the clinical utility of this thing is. We don't know, I am not sure exactly how I would program the first atrial shock if I got a DFT of nine. Do I have to put in a DFT of 18? I think there is a lot of learning curve that we are going to have to do on this and yes, I do think that putting in that 30 second delay before you can actually even start to get therapies may actually

decrease their chances of success.

I think all the patients in the clinical trial had to have a 30 second or a one minute delay before they could get therapies. They may improve their successes if they don't have to program that in.

DR. BRINKER: But it may also allow for self-termination of these arrhythmias which we will admit can be very transient. One of the problems with this, it has so many capabilities, so many potential combinations and permutations of programming that for us to think that on the basis even of the extensive study they have done that we can come up with the right or wrong opinion about how it should be programmed is just not feasible.

DR. SIMMONS: I am going to cut this off and ask for a recommendation.

DR. HARTZ: Besides, I am leaving and we won't have a quorum.

DR. SIMMONS: Does anybody feel comfortable making a recommendation?

DR. STUHLMULLER: So as a point of clarification, the panel is comfortable with the questions, having addressed all the issues?

Dr. SIMMONS: We have actually addressed all of these issues in our discussion.

DR. STUHLMULLER: Then we need to reopen the public hearing. Is there anybody from the public that would like to get

up and comment relative to the file? Is there anybody from FDA that would like to comment?

DR. SIMMONS: Is there something we should answer before we go on? Are you happy? You are happy, okay.

DR. STUHLMULLER: Would the sponsor like to make a comment?

DR. STANTON: In the interest of time, I will try to be brief, but I appreciated a lot of the discussion that went on. You raised some very important points and I just want to clarify some things. First off, I do want to reemphasize that the data we showed I think showed that there was no increase in mortality and supported that. This is a safe device. Move on from there.

A question was raised about the clinical utility. I would just ask you to keep in your mind what goes on in approval of drugs for atrial fibrillation. I don't know of any drug that has ever been shown to have clinical utility though they have been shown to terminate and prevent to some extent. I think we are in an analogous type of situation.

There is an incremental benefit to the VT/VF patient that this device provides. Remember, this is a ventricular defibrillator that we believe has incremental benefit or termination or prevention of atrial arrhythmias.

There was a question about removing the at-risk of developing atrial tachycardia for atrial fibrillation. I think that there are some studies out there. I won't get into it in

the interest of tie where people can do a risk assessment as to which patients are at an increased risk. Our study included people who had concomitant atrial tachyarrhythmias, the VT/AT group, and also people in the VT only group who were the VT/VF only patients.

As regards FDA question number four, sorry, number three, a question about should the Jewel AF be labeled as contraindicated for patients who do not have ventricular arrhythmias. Contraindicated we believe is something that should be reserved for something that has been shown to be harmful and there is maybe more appropriate wording if you wish to use such as a warning but we don't feel that the device is contraindicated since the device was never tested in the patients without VT and VF.

Regarding 27 joules delivered and stored, I think that is an important issue to be aware of. Twenty-seven joules delivered in this device is equivalent, we have stored of about 29 joules. That is similar to other, the same as other devices that are marketing and certainly appreciate that there be consistency in labeling.

Regarding FDA question number five about the pro-arrhythmia episode with 50 herz burst, that was one episode that occurred and I also ask you to keep in mind about pro-arrhythmia with drugs that are treated for atrial fibrillation. Most drugs having a pro-arrhythmic rate greater than one percent. Along

those lines I believe the question came up about high frequency burst not attaining the 50 percent threshold. The 50 percent threshold was not applied to an individual therapy by itself as Dr. BRINKER pointed out. That was for non-shock therapies as a group. We believe it is important that high frequency bursts provides an incremental benefit for 24 percent of the time that it was used. It prevented a shock from having to be delivered. That 24 percent effectiveness is based on a definition that the arrhythmia had to terminate within 32 cycle lengths. I will stop if you want to go ahead and reach a vote.

DR. HARTZ: You want us to vote, you gotta stop or else there is no quorum.

DR. BRINKER: Can I make a motion? I make a motion that we approve the device with all the labeling statements that we have previously suggested in which the FDA -

DR. STUHLMULLER: I have got to read the recommendation options.

DR. BRINKER: How about if we say let the FDA work out the -

DR. SIMMONS: No, he has got to read it.

DR. STUHLMULLER: All right. The Medical Device Amendments to the federal Food and Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel and designated medical device premarket approval

applications that are filed with the agency.

The PMA must stand on its own merits and the recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of intended use outweigh any probable risk. Effectiveness is defined as reasonable assurance that in a significant portion for the population the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

The recommendation options for the vote are as follows:

1. Approval if there are no conditions attached.

2. Approval but with conditions. The panel may recommend that the PMA be found approvable subject to specific conditions such as physician or patient education, labeling changes or further analysis of existing data. Prior to voting all the conditions should be discussed by the panel.

3. Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. SIMMONS: So what you probably want to do is make a motion to approve with conditions. Vote on that.

DR. BRINKER: Okay. I make a motion that we approve with conditions.

(Second from the floor.)

DR. GILLIAM: Do you want to list the conditions?

DR. SIMMONS: The conditions would be number one, that the changes in labeling as discussed and agreed in this meeting which can be obtained from the transcripts be added to the labeling of the device and number two that -

DR. GILLIAM: That the 6943 lead not be part of the system.

DR. BRINKER: You know, I was going to, I was just going to suggest that we need to address that lead. It is already approved for ventricular use. It could be used off-label but I would want one of two things, either a postmarket surveillance on that lead specifically or non-approval with the requirement to do a bigger IDE study.

DR. GILLIAM: Why don't you approve it without that lead and we can address it.

DR. BRINKER: Okay. I think that the suggestion was made that we deal with the defibrillator, the ICD, as separate

from the 6943 for right now and I think that is, is that doable? Or are you treating this as one system?

DR. STUHLMULLER: I am sorry, say the question again.

DR. BRINKER: I would like to distinguish between the ICD itself and the atrial, approval for the atrial use of the 6943 lead.

DR. STUHLMULLER: You are asking whether you can approve it but exclude the use of that lead with the system?

DR. BRINKER: Discuss that separately.

DR. STUHLMULLER: Wolf, do you want to comment?

DR. SAPIRSTEIN: This was presented as a system. I think it has got to be discussed and voted as a system.

DR. STUHLMULLER: I am not sure I quite understand. That it is a commercially marketed lead that was used in a different way so I mean -

DR. SAPIRSTEIN: They are searching for an additional indication for that lead and I don't think, I mean, there is two issues here.

DR. GILLIAM: The question is whether the device and I think it would be okay to approve the device with or without the lead but I think the use of that lead has not been demonstrated to be, I mean, unless we are willing to accept a five percent dislodgement rate in the atrium.

DR. SIMMONS: I mean, I don't know. He stunned me. I was asking for a one-month prohibition and now you are asking to

drop it from the study altogether.

DR. GILLIAM: I will retreat.

DR. BRINKER: I think that the issue is we need more data on that lead and one way of doing it is for postmarket thing. The other way is to say, look, it is already approved for the ventricle. We need more good data to approve it for the atrium. If people want to use it off-label for the atrium, they can do what they want.

DR. GILLIAM: But make them do a study with this lead. I mean, it doesn't have to go just in the atrial defibrillator. It can go in any defibrillator in effect. I mean, it can go in a dual chamber defibrillator and it can be used. It doesn't have to go only in the afib defibrillator so I think if the lead is effective, it ought to not take a lot of leads, implants to show that it is.

DR. SAPIRSTEIN: I am sorry. This is being presented as a system and it should be reviewed as such and recommendations made on that basis but perhaps we should ask Mis Terry what the routine is for the review of these devices, both IADs and pacemakers.

DR. STUHLMULLER: I think it is clarification, and I think the sponsor would, do you intend to market this as a system? I mean, is this lead going to come up and have, I mean, I understand that it is a marketed lead. Do you expect to get an additional indication for use for that lead from this study?

DR. CONNOLLY: That was our intent. This lead as you mentioned is approved in the ventricle of the 7250 Jewel AF does not require this lead for the system so from that standpoint it is not a requirement of the system but it is a lead that we would like to use with the Jewel AF as an option.

DR. STUHLMULLER: All right. So that is different in the sense of what we do with single pass systems where the pulse generator and the lead are labeled to be used together as a system.

DR. CONNOLLY: Right, this is not that situation.

DR. STUHLMULLER: So for clarification then, just to be correct, it is an additional indication for an approved device to be used in conjunction with the investigational device.

DR. CONNOLLY: We only have 96 leads, 96 implanted and we are basically saying 95 implants constitutes an ability to get a new indication for the lead implant.

DR. DOMANSKI: Right now it looks like the lead doesn't work very well so the bottom line is you can do one of three things. You can either disapprove the entire system, you can approve the system and ask for postmarket surveillance and see how it does. I mean, it is only 96. It is a little hard to know whether that is just bad luck, too. Or you can, maybe you can approve the device but not permit them to use that lead. I mean, it seems like there are only three options, gentlemen.

DR. BRINKER: Do they have further implants since the

cut-off date or is there a mechanism for, I think we need more data. I would be happy getting it postmarket surveillance.

DR. STUHLMULLER: You need to make your recommendation based on the data that is in the PMA that you have available for review, not any subsequent data that may or may not be in the file that has not been presented.

DR. SIMMONS: See, what you are actually asking also I think is if you improve the device with the indications for the lead, then they have got to come back with another 510K or some other kind of -

DR. BRINKER: They come back with the same ID or an ID supplement. Let's make it, the modification I would like is postmarket surveillance of the lead.

DR. DOMANSKI: How about a condition of approval? At this point there is a motion that has been made that has been seconded so from a procedural point of view that is a major motion. You can now make a subsidiary motion of which one type is a motion to amend. So what you need to do is make a motion that identifies the conditions of approval which would then be seconded, could be seconded and then you would potentially vote on the composite of the major amended which has been modified by the subsidiary amendment.

DR. BRINKER: I would like to do that. I would also suggest that in the next handouts we get are Roberts Rules of Order.

DR. DOMANSKI: I ill second his motion to amend.

DR. BRINKER: And the amendment would be -

DR. STUHLMULLER: Well, first you have got to put a motion out before you second it.

DR. BRINKER: I move that we amend my previous motion of approval and it would be to make the approval conditional upon postmarket surveillance demonstrating further the safe, well I can't say safety, but the performance of the 50 herz burst and the 6943 atrial defibrillator lead.

DR. DOMANSKI: I ill second that. And there were revisions to the labeling as well.

DR. BRINKER: But they are the same.

DR. STUHLMULLER: They are in the original motion.

DR. BRINKER: This is just an amendment.

DR. SIMMONS: Let me write them down. The conditions or the amendments you are suggesting are changes in the labeling as we have agreed as from the transcripts and number two that there be a condition of approval that a 100-leads be followed for six months to determine dislodgement rate and chronic thresholds and other complications of implantation. And number two -

DR. BRINKER: Or not only implantation but of function.

DR. SIMMONS: Okay. And number two -

DR. BRINKER: That the 50 herz burst therapy to -

DR. SIMMONS: You have to give them a patient number. How may patients over a period of time?

DR. BRINKER: Oh, I think the same number of patients. Same group of patients.

DR. STUHLMULLER: You could potentially agree in principle that additional data is required and you are going to leave it up to the sponsor and the FDA and/or the sponsor and the FDA in conjunction with a homework assignment to panel members to work out the numbers. That is another option you have.

DR. BRINKER: But it is important that for the lead it be 100 new patients which is different because we want to see the implantation.

DR. SIMMONS: Okay, so the amendment would be then approval with the condition of changes to the labeling as described from the transcripts. And number two, that 100 new patients be followed for at least six months to determine the dislodgement rate and other functional characteristics of the lead and number there, that the 50 herz anti-tachy function be studied in a way to be determined by the FDA and possibly a homework assignment in conjunction with the members of the panel.

DR. BRINKER: Great.

DR. DOMANSKI: Second.

DR. STUHLMULLER: All right so you have a motion and a second. Now you can vote.

DR. BRINKER: I approve.

DR. CRITTENDEN: Aye.

DR. DOMANSKI: Approve.

DR. GILLIAM: Aye.

DR. SIMMONS: AYE.

DR. STUHLMULLER: Actually you don't get to vote as the acting chair so it is four to zero.

DR. SIMMONS: Okay, I guess we have to go by and you have to explain why you voted yes.

DR. BRINKER: The obvious thing is that this met the criteria for safe and effective ventricular defibrillation and it offers an elegant approach toward what I believe will be a major role in the future of non-pharmacologic therapy for atrial arrhythmias and I think that kind of thing should be pursued vigorously, investigationally.

DR. CRITTENDEN: I can't say that any better. I agree with DR. BRINKER's comments.

DR. DOMANSKI: Safety and efficacy demonstrated.

DR. GILLIAM: I feel the safety is demonstrated and the device does what the indication suggests it can do.

DR. SIMMONS: I get to empirically adjourn the meeting so we are adjourned.

(Whereupon the meeting was adjourned at 4:46 P.M.)